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Original article

Efficacy and safety of alirocumab 150 mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON

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ABSTRACT

Background: Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, given every 2 weeks (Q2W), significantly reduced low-density lipoprotein cholesterol (LDL-C) levels in Japanese hypercholesterolemic patients on background statin. We evaluated alirocumab 150 mg every 4 weeks (Q4W) in patients on lowest-dose statin or non-statin lipid-lowering therapy (LLT).

Methods: ODYSSEY NIPPON was a double-blind study conducted in Japanese patients with LDL-C ≥100 mg/dL (heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with coronary heart disease) or ≥120 mg/dL (non-familial hypercholesterolemia, Japan Atherosclerosis Society category III) on atorvastatin 5 mg/day or non-statin LLT. Patients were randomized (1:1:1) to subcutaneous alirocumab 150 mg Q4W, alirocumab 150 mg Q2W, or placebo for the 12-week double-blind treatment period (DBTP), followed by a 52-week open-label treatment period (OLTP). At entry into the OLTP, patients received alirocumab 150 mg Q4W, with possible up-titration to 150 mg Q2W at Week 24.

Results: Least-square mean percent change in LDL-C from baseline at Week 12 (primary efficacy endpoint) was −43.8% for alirocumab Q4W, −70.1% for Q2W, and −4.3% for placebo. During the OLTP, mean LDL-C change from baseline was −45.1% at Week 20, with a further reduction at Week 36, with achieved levels maintained to Week 64. Percent of patients with ≥1 adverse event (DBTP) was 51.9% with alirocumab Q4W, 47.2% with Q2W, and 46.4% with placebo. Most common adverse events were infections and infestations (25.9%, 22.6%, 17.9%, respectively), gastrointestinal disorders (13.0%, 9.4%, 12.5%), nervous system disorders (5.6%, 7.5%, 10.7%), and general disorders and administration-site conditions (3.7%, 11.3%, 5.4%).

Conclusions: Hypercholesterolemic Japanese patients who tolerate only lowest-strength dose statin or non-statin LLT can achieve robust LDL-C reduction with alirocumab 150 mg Q4W, in addition to their current LLT. Alirocumab 150 mg Q4W dosing was efficacious and generally well tolerated without new safety concerns.

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Introduction

Cardiovascular disease (CVD) is the second most common cause of death in Japan [1]. Whereas mean serum cholesterol levels are decreasing in some countries, they are rising in Japan [2]. Reduction of elevated low-density lipoprotein cholesterol (LDL-C) – one of the most important modifiable risk factors for CVD [3] – is therefore essential in Japan.

The clinical response to statins is more sensitive in Asian than in Western populations, leading to lower-approved dosage strengths in Japan [4–7]. A sizable proportion of treated high-risk Japanese patients do not, however, achieve the recommended LDL-C goals [8–11]. In an analysis based on the Japanese Medical Data Vision database in 33,325 high cardiovascular risk patients, 45% of whom were receiving lipid-lowering therapy (LLT; 42% with a statin), 58% of patients with a recent acute coronary syndrome or other coronary heart disease achieved the Japan Atherosclerosis Society (JAS) guideline-recommended LDL-C target of <100 mg/dL [8]; only 1% of the patients on LLT were on a high-intensity statin and the use of combination therapy was low. Reasons for not using the higher dose of a statin or combination LLT include patient intolerance to these medications and physician preference. An alternative approach to lipid lowering is therefore necessary in patients who are unable to tolerate statins and are not adequately controlled with non-statin LLTs or the lowest-strength dose of statins.

Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9). Alirocumab gained manufacturing and marketing approval in Japan in June 2016 [12]. Alirocumab at doses of 75 mg or 150 mg every 2 weeks (Q2W) reduces LDL-C levels by 44–72% in patients with hypercholesterolemia with or without statin background treatment [13–22]. Alirocumab 150 mg every 4 weeks (Q4W) was identified, in a study conducted outside Japan [23], as a potential dosing regimen in patients with hypercholesterolemia who did not receive statin treatment. The combination of statin plus alirocumab Q2W led to persistent reductions in LDL-C over the dosing interval [14,15,18,21], but these reductions were not fully sustained when alirocumab was given Q4W [13,15]. Statin treatment increases free PCSK9 concentrations [24], resulting in higher target-mediated clearance of alirocumab and a reduced duration of effect [25]. Ezetimibe and fenofibrate also appear to increase free PCSK9 concentrations, but the effect is much smaller [25], making the Q4W regimen a feasible option as monotherapy and in patients on non-statin LLT.

The aim of the ODYSSEY NIPPON study [26] was to explore the alirocumab 150 mg Q4W regimen in Japanese patients with hypercholesterolemia who are on the lowest-strength dose of atorvastatin (5 mg/day) or are receiving a non-statin LLT (including diet-therapy alone). The primary objective was to demonstrate the reduction of LDL-C level by alirocumab 150 mg Q4W, or 150 mg Q2W, vs. placebo after 12 weeks of treatment. The secondary objectives were to determine the effect of alirocumab on other lipid variables, the safety and tolerability of alirocumab, and the long-term safety in patients receiving open-label alirocumab.

Methods

ODYSSEY NIPPON was a randomized, double-blind, placebo-controlled, parallel-group phase 3 study conducted in 163 patients recruited at 30 active sites in Japan. The first patient was enrolled in November 2015 and the last patient was enrolled in October 2016 (http://clinicaltrials.gov/NCT02584504).

The study methods have been published [26]. Eligible patients (age ≥20 years) had heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (non-FH), were on the lowest-strength dose of atorvastatin (5 mg/day) or were receiving a non-statin therapy (fenofibrate, bezafibrate, ezetimibe, or diet-therapy alone), and had not achieved recommended LDL-C levels according to the JAS guidelines [27]. Patients also had one or more documented reason to explain why statin therapy was not appropriate or why the lowest strength of statin dose could not be increased. All patients with heFH (diagnosed by genotyping or clinical criteria [28,29]) were eligible. Patients with non-FH were to have a history of documented coronary heart disease, or a history of diseases or other risk factors classified by the JAS as primary prevention category III (i.e. ischemic stroke, peripheral artery disease, diabetes mellitus, or chronic kidney disease) [27].

The study was performed according to the 18th World Medical Assembly and all applicable amendments laid down by the World Medical Assemblies, and the International Conference on Harmonization guidelines for good clinical practice, all applicable laws, rules, and regulations. The protocol was approved by the institutional review boards of participating centers. All patients provided written informed consent.

Intervention

The study consisted of a run-in period of 4 weeks, a screening period of up to 3 weeks, a double-blind treatment period (DBTP) of 12 weeks, and an open-label treatment period (OLTP) of 52 weeks. During the DBTP, patients were randomized, with a 1:1:1 allocation ratio, to receive alirocumab subcutaneously (SC) 150 mg Q4W (alternating with placebo to maintain the blind), alirocumab 150 mg SC Q2W, or placebo SC for alirocumab Q2W. Patients were stratified according to background statin (presence or absence); patients who were not on statins were further stratified by background fibrate/ezetimibe therapy or diet-therapy alone. From Week 12 onwards (OLTP), all patients received alirocumab 150 mg SC Q4W, with up-titration at Week 24 to alirocumab 150 mg Q2W for patients not reaching the LDL-C goal at Week 20. Open-label injections could be administered by patients/designated persons at their home.

Key study endpoints and assessments

The primary efficacy endpoint was the percentage change in calculated LDL-C from baseline to Week 12 using all LDL-C measurements, regardless of adherence to treatment [intention-to-treat (ITT) analysis]. Key secondary efficacy endpoints included percentage change in calculated LDL-C from baseline to Week 12 (on-treatment analysis); percentage change in calculated LDL-C from baseline to average Week 10–12 (ITT/on-treatment analysis); percent change from baseline to Week 12 in apolipoprotein B (ITT/on-treatment analysis), non-high-density lipoprotein cholesterol (non-HDL-C) (ITT/on-treatment analysis), total cholesterol (ITT analysis), lipoprotein(a) (ITT analysis), HDL-C (ITT analysis), fasting triglycerides (ITT analysis), apolipoprotein A-1 (ITT analysis); and the proportion of patients who reached the LDL-C goal at Week 12 (ITT/on-treatment analysis).

Safety and tolerability were assessed throughout the treatment periods by analyzing adverse-event reports (including adjudicated cardiovascular events), laboratory results, and vital signs. Laboratory analyses for all safety variables were performed by a central laboratory, as detailed elsewhere [26].

Statistical analysis

The primary efficacy analysis population comprised the ITT population (randomized population with an evaluable primary efficacy endpoint). The on-treatment (modified ITT) population

Table 1
Baseline characteristics (randomized patients).

Characteristic	Alirocumab 150 mg Q4W (n = 54)	Alirocumab 150 mg Q2W (n = 53)	Placebo Q2W (n = 56)
Age, years, mean ± SD	62.6 ± 9.8	63.6 ± 10.4	64.6 ± 10.0
Men, n (%)	33 (61.1)	33 (62.3)	37 (66.1)
Body mass index (kg/m^2), mean (SD)	25.8 ± 3.9	26.4 ± 4.7	25.6 ± 4.0
Type of hypercholesterolemia, n (%)			
Heterozygous FH	11 (20.4)	13 (24.5)	14 (25.0)
Non-FH	43 (79.6)	40 (75.5)	42 (75.0)
Cardiovascular history and risk factors, n (%)			
Myocardial infarction	8 (14.8)	6 (11.3)	6 (10.7)
Unstable angina	1 (1.9)	11 (20.8)	4 (7.1)
Coronary revascularization procedure	9 (16.7)	16 (30.2)	13 (23.2)
Other clinically significant CHD	4 (7.4)	6 (11.3)	10 (17.9)
Ischemic stroke (excluding cardiogenic cerebroembolism)	1 (1.9)	5 (9.4)	1 (1.8)
Peripheral artery disease	0	0	1 (1.8)
Chronic kidney disease	6 (11.1)	10 (18.9)	9 (16.1)
Diabetes mellitus	30 (55.6)	32 (60.4)	28 (50.0)
Hypo HDL cholesterolemia	0	2 (3.8)	0
Family history of premature CAD	2 (3.7)	8 (15.1)	1 (1.8)
Impaired glucose tolerance	3 (5.6)	2 (3.8)	2 (3.6)
Lipid parameters, mean ± SD or median (interquartile range)			
LDL-C (Friedewald formula) (mg/dL)	154.2 ± 59.5	149.2 ± 31.1	149.4 ± 32.6
Range	94:469	96:225	105:245
Apolipoprotein B (g/L)	126.2 ± 41.6	123.4 ± 20.2	123.9 ± 20.5
Total cholesterol (mg/dL)	240.2 ± 61.2	236.0 ± 35.3	234.4 ± 37.1
Non-HDL-C (mg/dL)	184.9 ± 63.8	181.8 ± 32.3	180.1 ± 32.4
Lipoprotein (a) (mg/dL)	16.55 (7.70:34.80)	22.60 (10.70:44.80)	12.65 (8.45:23.05)
Triglycerides (fasted) (mg/dL)	140.5 (98.0:190.0)	159.0 (116.0:213.0)	150.5 (114.0:193.5)
HDL-C (mg/dL)	55.2 ± 11.7	54.2 ± 11.6	54.3 ± 10.1
Background lipid-lowering therapy at randomization, n (%)			
Statin therapy	19 (35.2)	18 (34.0)	19 (33.9)
Atorvastatin 5 mg/day	18 (33.3)	18 (34.0)	18 (32.1)
Atorvastatin 2.5 mg/day	1 (1.9)	0	1 (1.8)
Any LLT other than statins	26 (48.1)	26 (49.1)	27 (48.2)
Ezetimibe	7 (13.0)	14 (26.4)	11 (19.6)
Fibrate	19 (35.2)	12 (22.6)	16 (28.6)
Fenofibrate	9 (16.7)	4 (7.5)	6 (10.7)
Bezafibrate	10 (18.5)	8 (15.1)	10 (17.9)
Diet alone	9 (16.7)	9 (17.0)	10 (17.9)

CAD, coronary artery disease; CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SD, standard deviation; Q2W, every 2 weeks; Q4W, every 4 weeks.

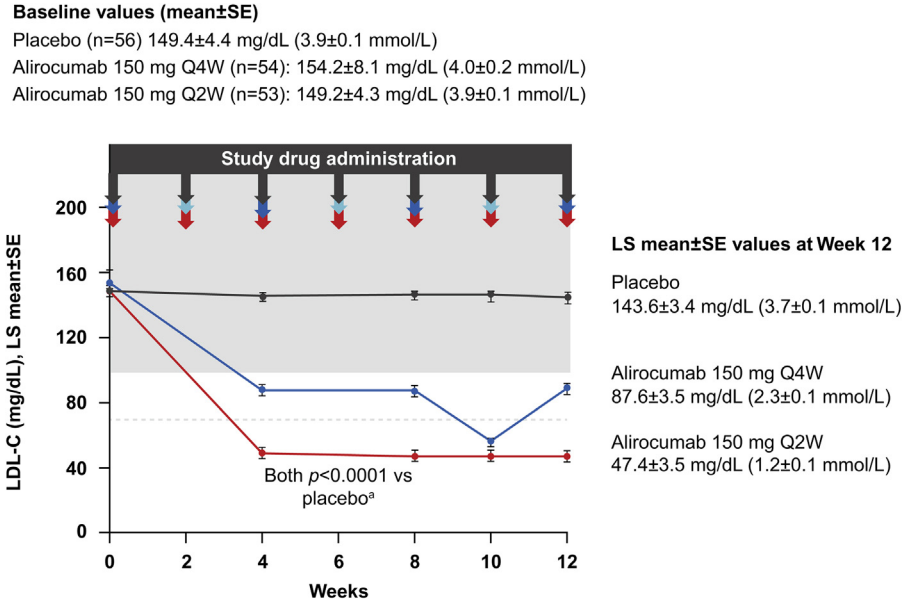

Fig. 1. LDL-C LS mean ± SE over time (ITT population) in patients on alirocumab 150 mg Q4W, alirocumab 150 mg Q2W, or placebo Q2W. Arrows indicate administration of study drug in each treatment group (pale-blue arrows indicate administration of placebo in the Q4W group). ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 2
Percent change from baseline to Week 12 in LDL-C, and from baseline to Week 12 (or averaged weeks 10–12 percent change) in secondary lipid variables.

	Alirocumab 150 mg Q4W	Alirocumab 150 mg Q2W	Placebo	Alirocumab 150 mg Q4W vs. placebo			Alirocumab 150 mg Q2W vs. placebo		
				LS mean difference ± SE (%)	97.5% confidence interval	*p*-value	LS mean difference ± SE (%)	97.5% confidence interval	*p*-value
Primary endpoint: LDL-C (calculated)[a]									
LS mean (SE) change from baseline (%)	−43.8 ± 2.2	−70.1 ± 2.3	−4.3 ± 2.2	−39.5 ± 3.1	−46.5 to −32.4	<0.0001	−65.8 ± 3.1	−72.9 to −58.7	<0.0001
Secondary lipid parameters, LS mean (SE) change from baseline (%)									
LDL-C[b] (Week 12)	−43.4 ± 2.1	−70.1 ± 2.2	−2.8 ± 2.1	−40.6 ± 3.0	−47.4 to −33.8	<0.0001	−67.4 ± 3.0	−74.2 to −60.5	<0.0001
LDL-C[a] (Weeks 10–12)	−54.2 ± 1.9	−69.9 ± 1.9	−3.7 ± 1.9	−50.5 ± 2.7	−56.6 to −44.5	<0.0001	−66.2 ± 2.7	−72.3 to −60.1	<0.0001
LDL-C[b] (Weeks 10–12)	−54.0 ± 1.9	−69.9 ± 1.9	−2.6 ± 1.9	−51.4 ± 2.6	−57.4 to −45.4	<0.0001	−67.3 ± 2.7	−73.3 to −61.3	<0.0001
Apolipoprotein B[a] (Week 12)	−32.2 ± 2.0	−57.9 ± 2.0	−6.0 ± 2.0	−26.2 ± 2.8	−32.5 to −19.9	<0.0001	−51.9 ± 2.8	−58.3 to −45.5	<0.0001
Apolipoprotein B[b] (Week 12)	−31.8 ± 2.0	−58.0 ± 2.0	−4.6 ± 1.9	−27.2 ± 2.8	−33.5 to −20.9	<0.0001	−53.4 ± 2.8	−59.7 to −47.1	<0.0001
Non-HDL-C[a] (Week 12)	−36.2 ± 2.0	−61.1 ± 2.0	−4.9 ± 2.0	−31.3 ± 2.8	−37.7 to −25.0	<0.0001	−56.2 ± 2.8	−62.5 to −49.8	<0.0001
Non-HDL-C[b] (Week 12)	−35.9 ± 1.9	−61.1 ± 2.0	−3.5 ± 1.9	−32.4 ± 2.7	−38.6 to −26.3	<0.0001	−57.6 ± 2.7	−63.8 to −51.4	<0.0001
Total cholesterol[a] (Week 12)	−25.8 ± 1.5	−44.7 ± 1.6	−3.3 ± 1.5	−22.5 ± 2.2	−27.4 to −17.6	<0.0001	−41.4 ± 2.2	−46.4 to −36.5	<0.0001
Lipoprotein(a)[a,c] (Week 12)	−31.7 ± 3.3	−49.6 ± 3.3	1.3 ± 3.3	−32.9 ± 4.6	−43.4 to −22.5	<0.0001	−50.9 ± 4.7	−61.5 to −40.3	<0.0001
HDL-C[a] (Week 12)	7.7 ± 1.8	9.9 ± 1.8	2.0 ± 1.8	5.7 ± 2.5	0.0 to 11.3	0.0241	7.8 ± 2.5	2.1 to 13.5	0.0022
Triglycerides (fasted)[a,c] (Week 12)	−0.6 ± 3.7	−18.0 ± 3.8	−6.4 ± 3.7	5.9 ± 5.3	−5.9 to 17.7	0.2645	−11.6 ± 5.3	−23.5 to 0.4	0.0299
Apolipoprotein A-1[a] (Week 12)	6.8 ± 1.6	9.1 ± 1.7	2.9 ± 1.6	3.9 ± 2.3	−1.2 to 9.0	0.0884[d]	6.2 ± 2.3	1.0 to 11.4	0.0076[d]

HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; Q2W, every 2 weeks; Q4W, every 4 weeks.
[a] ITT population.
[b] On-treatment population (modified ITT).
[c] Combined estimate obtained by combining adjusted means (SE) from robust regression model analyses of the different imputed datasets (multiple imputation).
[d] *p*-values provided for descriptive purposes.

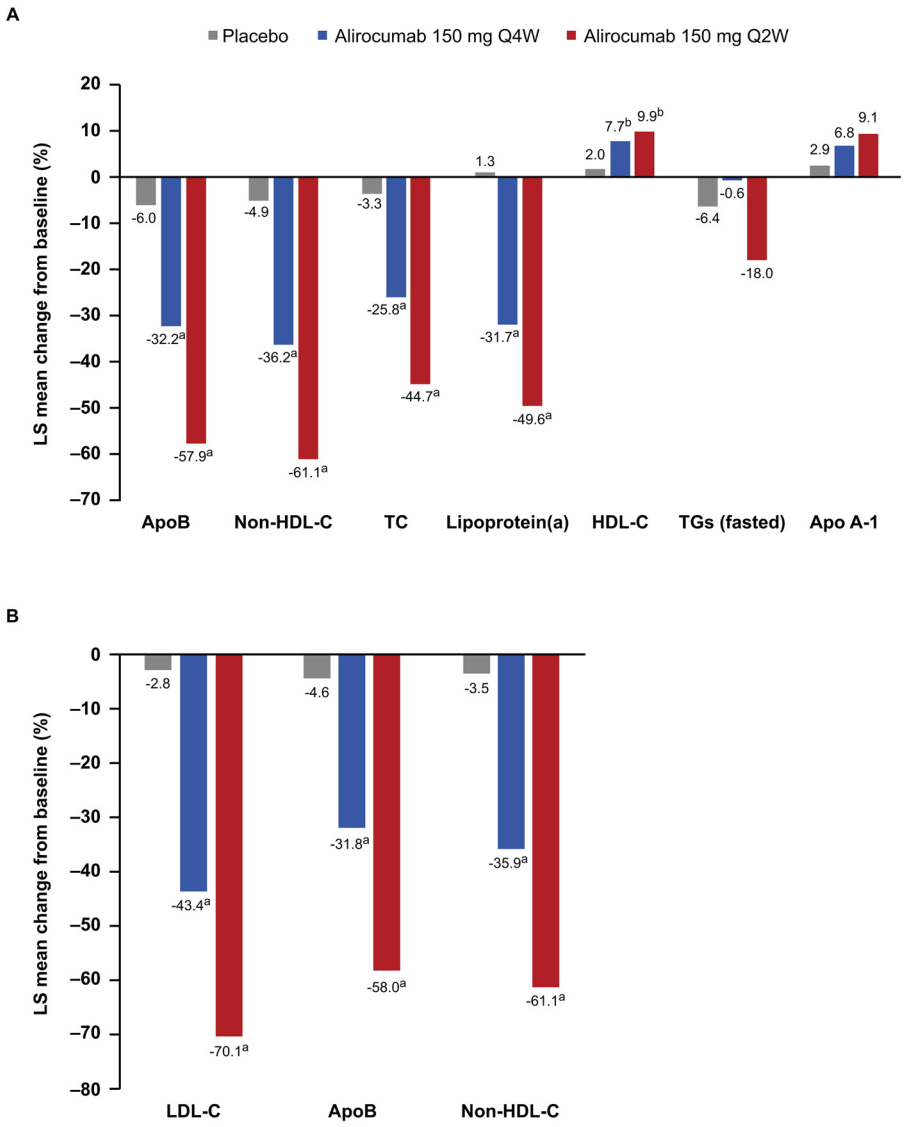

Fig. 2. Secondary outcomes: percent change from baseline to Week 12: (A) ITT population; and (B) on-treatment (modified ITT) population. [a]$p < 0.0001$ vs. placebo; [b]$p < 0.025$ vs. placebo (Bonferroni adjustment used to handle multiple comparisons). Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; TC, total cholesterol; TGs, triglycerides.

was defined as the randomized population who received the double-blind injection and had an evaluable primary efficacy endpoint during the efficacy DBTP. The safety population comprised the randomized population who received at least one dose of the study medication. The OLTP population comprised the randomized population who received the open-label study medication.

The primary efficacy endpoint was analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. The model included the fixed categorical effects of treatment group, time point (4, 8, 10, 12 weeks), stratification factor of statin, treatment-by-time-point interaction and statin-by-time-point interaction, and the continuous fixed covariates of baseline calculated LDL-C value, and baseline value-by-time-point interaction.

Continuous secondary endpoints with a normal distribution were analyzed using the MMRM model. Continuous endpoints with a non-normal distribution and binary secondary endpoints were analyzed using a multiple imputation approach followed by robust or logistic regression, respectively. Bonferroni adjustment and a hierarchical procedure were used to handle multiplicity.

The data for the safety analysis are reported descriptively. The analysis was conducted in two steps. The first step concerned the final efficacy and safety analyses, and was conducted when all patients had been randomized and had at least all of their data up to Week 24 (including 12 weeks DBTP and 12 weeks OLTP) collected and validated. The second step was the final analysis of the safety endpoints and exploratory efficacy assessment during the OLTP, conducted at the end of the study with all data including that from the OLTP.

The analysis was performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Study population

Of 163 eligible patients, 54 were randomized to receive alirocumab 150 mg Q4W group, 53 to receive alirocumab 150 mg Q2W, and 56 to receive placebo (Online Fig. 1). All 163 patients received the study treatment and were included in the primary efficacy analyses and the adverse-event analysis at

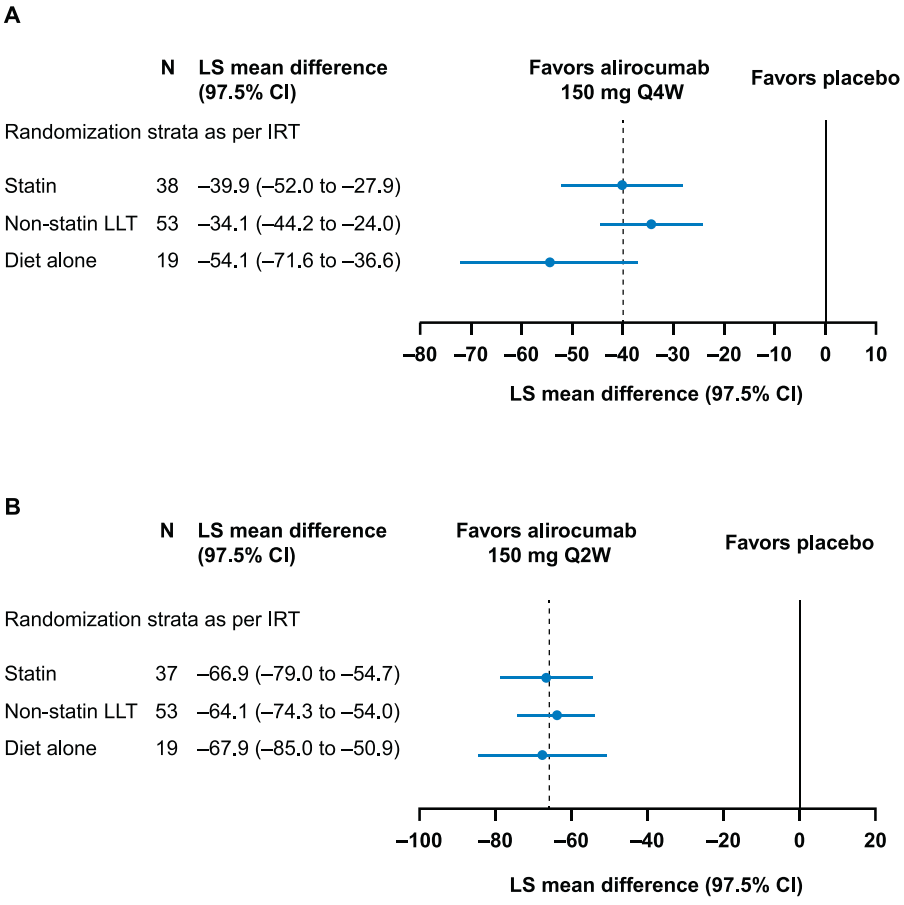

Fig. 3. Percent change from baseline in calculated low-density lipoprotein cholesterol at Week 12 in the (A) 150 mg Q4W group and (B) 150 mg Q2W group (intention-to-treat population), per randomization strata. CI, confidence interval; IRT, interactive response technology; LLT, lipid-lowering therapy; LS, least squares; Q2W, every 2 weeks; Q4W, every 4 weeks.

12 weeks. Three patients discontinued the study treatment during the DBTP, two (3.8%) in the alirocumab 150 mg Q2W group and one (1.8%) in the placebo group. At Week 12, the primary efficacy endpoint was missing for 1 patient (1.9%) in the alirocumab 150 mg Q4W group, 2 patients (3.8%) in the alirocumab 150 mg Q2W group, and 1 patient (1.8%) in the placebo group. These missing values were accounted for by the MMRM model.

A total of 158 patients entered the 52-week OLTP, during which all patients were started on alirocumab 150 mg Q4W with the possibility of up-titration to Q2W at Week 24; 146 patients completed the OLTP and were included in the long-term safety analysis.

Patient baseline characteristics were well balanced across treatment groups (Table 1). The mean ± standard deviation (SD) age of the study population was 63.6 ± 10.1 years and 63.2% were men.

Overall, 82.8% of patients had a history of CVD or cardiovascular risk factors; 28.2% had a history of coronary heart disease, 23.3% had heFH, 55.2% had diabetes mellitus, 15.3% had chronic kidney disease, 4.3% had a history of ischemic stroke, and 0.6% had a history of peripheral artery disease. The overall mean ± SD calculated LDL-C at baseline was 150.9 ± 42.8 mg/dL (3.91 ± 1.11 mmol/L). The most common reasons pertaining to low-dose statin treatment or prescription of non-statin LLT were a history of statin-related side effects, treatment with medications such as a CYP34A inhibitor and fibrates, and renal dysfunction (Online Table 1).

Exposure to study drug injections during the DBTP was similar across treatment groups, with a mean exposure of 11.9 weeks.

Lipid and lipoprotein response

For the primary ITT efficacy analysis, least square (LS) mean - ± standard error (SE) percent changes in LDL-C concentration from baseline to Week 12 were −43.8 ± 2.2% in the alirocumab 150 mg Q4W group and −4.3 ± 2.2% in the placebo group, with a difference between groups of–39.5% (97.5% CI −46.5 to–32.4; $p < 0.0001$) (Fig. 1 and Table 2). The effect of alirocumab 150 mg Q4W was consistent irrespective of stratification factor [statin presence: LS mean difference −40.0% (97.5% CI −52.1 to −27.8); statin absence: LS mean difference −39.2% (97.5% CI −48.0 to −30.4); interaction $p = 0.91$]. LS mean (SE) percent change in LDL-C concentration from baseline to Week 12 in the alirocumab 150 mg Q2W group was −70.1 ± 2.3%, with a difference vs. placebo of −65.8% (97.5% CI −72.9 to −58.7; $p < 0.0001$) (Fig. 1 and Table 2). The effect of alirocumab 150 mg Q2W was consistent irrespective of stratification factor [statin presence: LS mean difference −66.9% (97.5% CI −79.1 to −54.6); statin absence: LS mean difference −65.2% (97.5% CI −74.0 to −56.4; interaction $p = 0.80$)].

Percent change in calculated LDL-C from baseline to average Week 10–12 was −54.2 ± 1.9% for alirocumab 150 mg Q4W, −69.9 ± 1.9% for alirocumab 150 mg Q2W, and −3.7 ± 1.9% for placebo in the ITT analysis. LS mean percent changes at Week 12 in secondary efficacy endpoints are shown in Fig. 2 and Table 2. Percent change from baseline in calculated LDL-C at Week 12 was consistent across randomization strata (Fig. 3A and B).

At Week 12, 85.2% of patients on alirocumab 150 mg Q4W and 96.2% on alirocumab 150 mg Q2W had achieved the LDL-C goal vs.

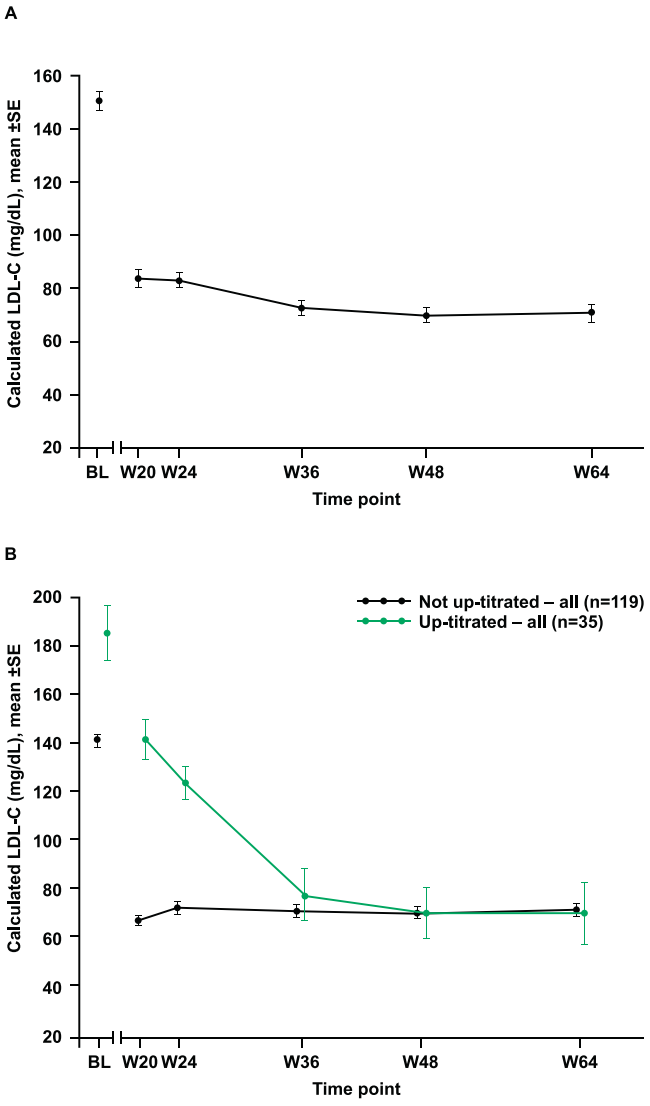

Fig. 4. Calculated LDL-C (mean ± SE) over time in the (A) OLTP population and (B) OLTP population according to up-titration status (OLTP). BL, baseline; LDL-C, low-density lipoprotein cholesterol; OLTP, open-label treatment period; SE, standard error; W, week.

14.3% on placebo (both $p < 0.0001$ vs. placebo) in the ITT analysis. Similar results were observed in the on-treatment analysis (85.2%, 96.2%, and 10.8%, respectively; both $p < 0.0001$ vs. placebo).

Least-square mean percent change in LDL-C from baseline at Week 12 in patients with coronary artery disease was −49.6% for alirocumab Q4W, −67.9% for Q2W, and 0.3% for placebo. Corresponding data for patients without coronary artery disease are −42.3% for alirocumab Q4W, −71.1% for Q2W, and −6.4% for placebo.

A mean ± SD −45.1 ± 21.6% LDL-C reduction was observed from baseline to the first OLTP measurement (Week 20). The dose of alirocumab was increased from 150 mg Q4W to 150 mg Q2W at Week 24 in 35 patients (22.7%) resulting in a further LDL-C reduction between Week 24 and Week 36. The reduction in LDL-C was maintained over the course of the OLTP and the achieved absolute LDL-C level was 71.3 ± 42.1 mg/dL at Week 64 (Fig. 4A). Among patients not achieving the target LDL-C level at Week 20, up-titration to 150 mg Q2W led to a substantial and sustained reduction in LDL-C (Fig. 4B). Over three-quarters (76.9%) of the patients on alirocumab 150 mg Q4W achieved the JAS LDL-C goal for very high-risk patients [27] at Week 20. The proportion of patients who achieved the JAS LDL-C goal rose to 89.5% at Week 36, after up-titration at Week 24 in those with hypercholesterolemia, and was sustained through Week 64 (Online Fig. 2).

Safety

During the DBTP, 51.9% of patients on alirocumab 150 mg Q4W, 47.2% on alirocumab 150 mg Q2W, and 46.4% on placebo reported the occurrence of an adverse event (Table 3). Four patients reported a serious adverse event, one on alirocumab 150 mg Q4W, two on alirocumab 150 mg Q2W, and one on placebo. One death occurred, due to non-small-cell lung cancer (in the alirocumab 150 mg Q2W group), and was not considered related to the study treatment; the only study-drug discontinuation during the DBTP was in the patient who died.

The most common classes of adverse events during the DBTP were infections and infestations (25.9% on alirocumab 150 mg Q4W, 22.6% on alirocumab 150 mg Q2W, and 17.9% on placebo), gastrointestinal disorders (13.0%, 9.4%, and 12.5%, respectively), nervous system disorders (5.6%, 7.5%, and 10.7%, respectively), and general disorders and administration site conditions (3.7%, 11.3%, and 5.4%, respectively). The most common types of adverse events (by preferred term level) were viral upper respiratory tract infection (14.8% on alirocumab 150 mg Q4W, 15.1% on alirocumab 150 mg Q2W, and 16.1% on placebo), non-cardiac chest pain (0%, 7.5%, and 1.8%, respectively), fall (0%, 1.9%, and 5.4%, respectively), dizziness (0%, 0%, and 5.4%, respectively), and pharyngitis (5.6%, 0%, and 0%, respectively). Local injection site reactions were reported in one patient (0.9%), in the alirocumab 150 mg Q4W group. There was no relevant difference between treatment groups on safety laboratory data during the DBTP (Table 3).

During the 52-week OLTP, 109 (69.0%) patients reported the occurrence of any adverse event (Table 4). Twelve patients (7.6%) reported a serious adverse event, none of which was fatal. Seven patients (4.4%) had an adverse event that led to treatment discontinuation. No new or unexpected safety findings emerged.

Discussion

In this study, hypercholesterolemic Japanese patients who were not receiving statin therapy or who tolerate only the lowest-strength dose of atorvastatin achieved clinically meaningful and statistically significant reductions in LDL-C at Week 12 with alirocumab 150 mg Q4W in addition to their existing LLT, including diet-therapy alone, compared with patients receiving LLT plus placebo for alirocumab. Most of the patients (85.2%) on the Q4W regimen achieved the JAS LDL-C goal [27] at Week 12. With the alirocumab 150 mg Q2W regimen, a reduction of 70.1% in LDL-C was achieved at Week 12, and 96.2% of patients achieved the JAS goal [27] for LDL-C. A consistent reduction in LDL-C from baseline was observed from the first measurement during the OLTP (Week 20), and decreased further at Week 36, due to the possible dose adjustment to 150 mg Q2W, and was maintained through Week 64. The alirocumab 150 mg Q4W and Q2W dosing regimens were generally well tolerated during the 12-week DBTP and the 52-week OLTP.

The reductions in LDL-C in this study are broadly consistent with the phase 3 ODYSSEY JAPAN study [22], which reported a 62.5% reduction at Week 24 in LDL-C with alirocumab 75 mg Q2W, with up-titration to 150 mg Q2W if Week 8 LDL-C was ≥100 mg/dL (heFH or non-FH with a history of coronary artery disease) or ≥120 mg/dL (JAS category III). The reduction in LDL-C was also sustained through Week 52 in ODYSSEY JAPAN. At Week 12, alirocumab treatment also resulted in beneficial reductions in apolipoprotein B, non-HDL-C, total cholesterol, and lipoprotein (a), and increases in HDL-C and apolipoprotein A-1. The

Table 3
TEAEs and laboratory variables (safety population) at 12 Weeks (DBTP).

	Alirocumab 150 mg Q4W (*n* = 54)	Alirocumab 150 mg Q2W (*n* = 53)	Placebo Q2W (*n* = 56)
Any TEAE, *n* (%)	28 (51.9)	25 (47.2)	26 (46.4)
Treatment-emergent SAE, *n* (%)	1 (1.9)	2 (3.8)	1 (1.8)
TEAE leading to death, *n* (%)	0	1 (1.9)	0
TEAE leading to treatment discontinuation during DBTP, *n* (%)	0	1 (1.9)	0
TEAE during DBTP leading to treatment discontinuation during open-label treatment period, *n* (%)	0	0	1 (1.8)
TEAEs (primary system organ class level) occurring in ≥5% of patients in any group, *n* (%)			
Infections and infestations	14 (25.9)	12 (22.6)	10 (17.9)
Gastrointestinal disorders	7 (13.0)	5 (9.4)	7 (12.5)
Nervous system disorders	3 (5.6)	4 (7.5)	6 (10.7)
General disorders and administration site conditions	2 (3.7)	6 (11.3)	3 (5.4)
Musculoskeletal and connective tissue disorders	3 (5.6)	3 (5.7)	4 (7.1)
Injury, poisoning and procedural complications	0	3 (5.7)	5 (8.9)
TEAEs (preferred term level) in ≥5% of patients in any group, *n* (%)			
Viral upper respiratory tract infection	8 (14.8)	8 (15.1)	9 (16.1)
Non-cardiac chest pain	0	4 (7.5)	1 (1.8)
Fall	0	1 (1.9)	3 (5.4)
Dizziness	0	0	3 (5.4)
Pharyngitis	3 (5.6)	0	0
Adjudicated cardiovascular event (any patient with treatment-emergent event), *n* (%)[a]	0	0	1 (1.8)
Laboratory parameters, *n* (%)			
Alanine aminotransferase >3 × ULN	0	0	0
Aspartate aminotransferase >3 × ULN	0	0	0
Bilirubin >1.5 × ULN	0	0	0
Creatine kinase >3 × ULN	0	0	0

DBTP, double-blind treatment period; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; Q2W, every 2 weeks; Q4W, every 4 weeks.
[a] Ischemia-driven coronary revascularization procedure.

Table 4
TEAEs and laboratory variables during the 52-week OLTP (OLTP population).[a]

	All patients (*n* = 158)
Any TEAE, *n* (%)	109 (69.0)
Treatment-emergent SAE, *n* (%)	12 (7.6)
TEAE leading to death, *n* (%)	0
TEAE leading to treatment discontinuation during open-label treatment period, *n* (%)	7 (4.4)
TEAEs (primary system organ class level) occurring in ≥5% of patients, *n* (%)	
Infections and infestations	77 (48.7)
Gastrointestinal disorders	31 (19.6)
Musculoskeletal and connective tissue disorders	26 (16.5)
Skin and subcutaneous tissue disorders	19 (12.0)
Injury, poisoning and procedural complications	19 (12.0)
Metabolism and nutrition disorders	12 (7.6)
Nervous system disorders	11 (7.0)
General disorders and administration site conditions	9 (5.7)
Renal and urinary disorders	9 (5.7)
Respiratory, thoracic and mediastinal disorders	9 (5.7)
Investigations	8 (5.1)
Psychiatric disorders	8 (5.1)
TEAEs (preferred term level) occurring in ≥5% of patients, *n* (%)	
Viral upper respiratory tract infection	54 (34.2)
Fall	11 (7.0)
Back pain	8 (5.1)
Adjudicated cardiovascular event (any patient with treatment-emergent event), *n* (%)[b]	1 (0.6)
Laboratory parameters, *n* (%)	
Alanine aminotransferase >3 × ULN	2/156 (1.3)
Aspartate aminotransferase >3 × ULN	2/156 (1.3)
Bilirubin >1.5 × ULN	0
Creatine kinase >3 × ULN	4/156 (2.6)

OLTP, open-label treatment period; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
[a] All patients received alirocumab 150 mg SC Q4W during the 52-week OLTP. At Week 24, a dose increase of alirocumab to 150 mg SC Q2W was automatically conducted through the interactive web response system in patients with heterozygous familial hypercholesterolemia (heFH) or non-FH with documented coronary heart disease if low-density lipoprotein cholesterol (LDL-C) was ≥100 mg/dL (2.59 mmol/L), and in non-FH category III patients if LDL-C was ≥120 mg/dL (3.10 mmol/L), at Week 20.
[b] Non-fatal myocardial infarction.

alirocumab 150 mg Q4W regimen resulted in a 31.7% reduction in lipoprotein(a), an independent predictor of coronary artery disease [22,30–32].

In our study, alirocumab was generally well tolerated, with no apparent imbalance in adverse events across treatment groups during the DBTP. Tolerability was maintained over the long term,

with the most frequent adverse events being viral upper respiratory tract infection during the OLTP.

Drug response to statins differs in Asian vs. Western populations, with Asians achieving similar reductions in LDL-C as Westerners at lower drug doses [4–7]. Body size appears to have limited effect on drug efficacy [33,34], whereas genetic variability, such as genetic polymorphism of metabolic enzymes or transporters, has a greater influence on the pharmacokinetic and pharmacodynamic properties of drugs [5,35]. Owing to these racial differences, lower statin treatment doses have been approved in Japan [4–7]. However, several studies have shown that a large proportion of high-risk Japanese patients do not achieve the recommended LDL-C goals [8–10,31]. According to a large study based on an electronic hospital-based claims database, only 56% of patients with a recent acute coronary syndrome and 51% with other coronary heart disease met the JAS [27] LDL-C target of <100 mg/dL. This failure was due in part to low rates of use of high-intensity statin therapy and of combination therapy [8]. The target population in ODYSSEY NIPPON was hypercholesterolemic Japanese patients who were on the lowest-strength dose of atorvastatin or were receiving non-statin LLT, including diet-therapy alone. In the prespecified analysis, regardless of the type of background LLT, treatment with alirocumab (Q4W or Q2W) led to substantial reductions in LDL-C across all subgroups.

The most frequent reason for not using a statin in this study, or for using only low-dose statin, was a history of statin-related side effects. Side effects from statin, particularly muscle symptoms [36,37], limit many patients from achieving optimal LDL-C levels [37–39]. The ODYSSEY CHOICE II study investigated alirocumab 150 mg SC Q4W (with possible up-titration to 150 mg Q2W at Week 12) vs. placebo in patients with hypercholesterolemia while receiving treatment with fenofibrate, ezetimibe, or diet-therapy alone, most of whom had reported statin-associated muscle symptoms. Alirocumab 150 mg Q4W (with up-titration to Q2W in 49.1% of patients) produced a 51.7% reduction in LDL-C from baseline, 63.9% of patients achieved their LDL-C targets, and alirocumab was generally well tolerated. On the basis of the data from these studies, alirocumab 150 mg Q4W may offer a suitable and effective clinical option in the management of Japanese patients who are not receiving statin therapy or who tolerate only the lowest-strength dose of atorvastatin.

Limitations

Study limitations include the 12-week DBTP. The dose of atorvastatin used (≤5 mg/day) is more conservative than in regions outside of Japan, limiting direct comparison of the results between studies conducted in other countries or regions. The putative effect of visit-to-visit variability in LDL-C levels on clinical outcomes has not been established.

Conclusions

Hypercholesterolemic Japanese patients can achieve robust LDL-C reductions with alirocumab 150 mg Q4W in addition to their prior LLT, including atorvastatin 5 mg/day, fibrate, ezetimibe, or diet alone. Alirocumab 150 mg Q4W, with a possible dose increase to 150 mg Q2W, offers an alternative, flexible dosing, and generally well-tolerated lipid-lowering regimen for Japanese patients who are unable to tolerate statins and are not adequately controlled with non-statin LLTs or who are on the lowest-strength dose of statin.

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Data availability

Qualified researchers may request access to patient level data and related study documents, from the primary clinical study, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

Conflict of interest

TT received a research grant from Amgen Astellas Biopharma K.K., scholarship grants from Daiichi Sankyo Company, Limited, Takeda Pharmaceutical Company Limited, Astellas Pharma Inc, Kissei KK and Shionogi & Co. Limited, honoraria for lecture fees from Bayer Yakuhin Limited, Pfizer Japan Limited, Takeda Pharmaceutical Company Limited, Astellas Pharma Inc, Kowa company Limited, Sanofi K.K., MSD K.K., Amgen Astellas Biopharma K.K. and Astra-Zeneca KK, fees for promotion materials from Daiichi Sankyo Company Limited, courses endowed from Kowa company Limited, MSD K.K., Bayer Yakuhin Limited, and Mochida Yakuhin KK.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.10.004.

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